NIEHS News

Where Bench and Field Sciences Meet: Molecular Epidemiology at NIEHS

There is a quiet corner in London, not far from the specialty shops and heavy traffic of Oxford Street, that is the site of the John Snow Pub. Nothing about this pub would catch the eye of the average passerby. But for epidemiologists it is a mecca, a memorial to one of their most famous colleagues. John Snow was a London physician in the mid-1800s who became a legend through one simple, dramatic act. During a local cholera outbreak, he made a map showing the geographic distribution of homes with cholera victims. He found that the affected homes were all in a neighborhood that drew drinking water from a particular pump on Broad Street. Snow removed the handle from the Broad Street pump (near where his namesake pub now stands), and the epidemic subsided.

In some ways, this story neatly captures the kind of work epidemiologists do. Patterns of disease in populations can provide useful clues about causes of the disease. Snow was able to prevent the spread of cholera while knowing nothing about the existence of a cholera bacillus. Even though he did not understand the underlying cause, Snow was able to take effective action because the link between the polluted water source and the outbreak of diseases was so direct and unambiguous. Today's public health problems are seldom so clear.

Most illness in the United States today is related to chronic diseases such as cancer, heart disease, diabetes, and diseases of aging. Often there is a long latency between a dangerous exposure (e.g., to asbestos) and the actual onset of disease. Also, multiple factors over time contribute to the risk of disease. Epidemiologists can no longer rely simply on patterns of disease to lead them to the sources of disease. They must know something about the biological mechanisms involved. Epidemiologists depend increasingly on the tools of the laboratory in carrying out their research. This is especially true for health studies that look for damage caused by low-level environmental contaminants.

Degenerative Neurologic Diseases

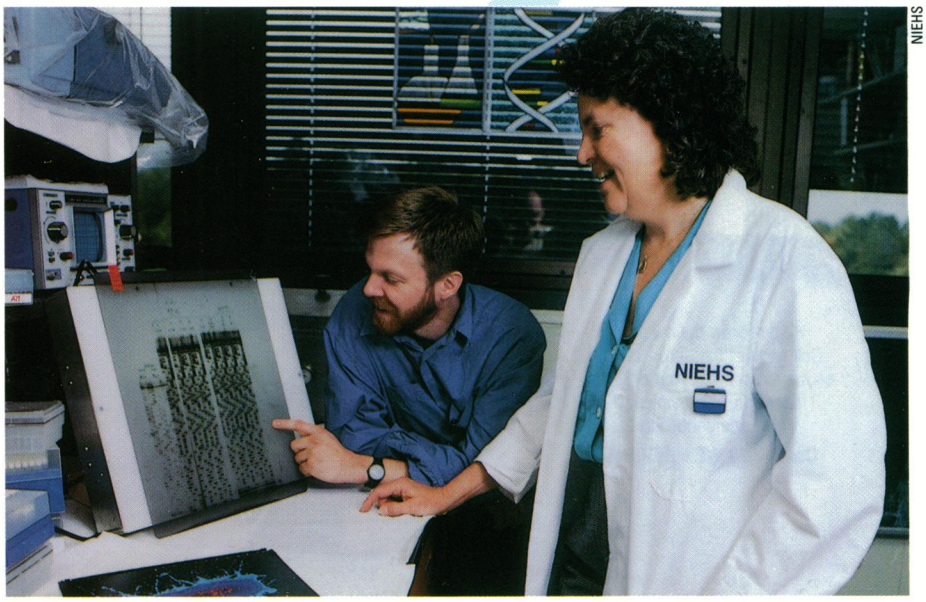
Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a devastating, progressive illness that leads to paralysis and death. Freja Kamel, senior staff fellow, is carrying out a study of ALS as part of a program to uncover environmental causes of neurologic diseases. One goal of the ALS study is to determine whether environmental neurotoxins such as lead might contribute to risk of the disease. This is a plausible biological hypothesis, but previous studies have been equivocal. A person's lifetime exposure to lead and other toxins is difficult to determine; previous studies have relied only on questionnaires.

Kamel's study takes advantage of a newly developed technique, X-ray fluorescence (XRF), to measure lead exposure. XRF uses extremely low levels of radiation to measure the lead absorbed in a person's bone tissue over his or her lifetime. XRF technology was developed partly with a research project grant and small business innovation research grants from NIEHS to private companies. Although XRF machines are a useful research tool, there are only a few in the world. Kamel has collaborated with researchers at Harvard Medical School who operate an XRF machine. Kamel and her colleagues will measure bone lead of patients at New England Medical Center newly diagnosed with ALS and of a comparison group of patients. Higher lead levels in the ALS patients would provide evidence that lead exposure over a lifetime may play a role in degenerative diseases of the central nervous system.

In addition, Kamel is storing blood specimens for genetic testing. With the recent advent of rapid and inexpensive genetic analysis, epidemiologists can begin to explore the combined effects of genetics and environmental exposures in large-scale studies. With the DNA specimens Kamel is storing, she and her colleagues will be able to study genes involved in repair of neurotoxic damage, protection against free radicals, or metabolism of excitotoxic neurotransmitters.

Cleft Lip and Palate

There is a rapidly growing list of genes that may play a role in disease susceptibility. People inherit variant forms of genes that control detoxification of toxic substances, form hormone receptors, and regulate metabolic pathways. In collaboration between NIEHS and the National Institute of Public Health in Norway, Allen Wilcox, chief of the Epidemiology Branch, is carrying out a study of genetic susceptibility to birth defects. Wilcox and his colleagues plan to enroll every baby born in Norway with cleft lip or palate over the next five years. Norway has an unusually well-organized system of birth registration and medical care that makes it possible to conduct a population-based study. When completed, this will be the largest study of facial clefts ever carried out. Mothers of cases and controls will be interviewed about environmental and occupational exposures, diet, medications, and other factors during pregnancy. Blood samples will be obtained from mothers and babies. Questionnaire information on possible hazardous exposures will be combined with assays of certain genetic alleles in stored samples to look for evidence that some mothers or infants may be genetically susceptible to the effects of specific environmental exposures.



NIEHS

Gene sleuths. Jack Taylor and Theodora Devereux hunt for clues to lung tumors in the p53 gene of uranium miners.

Cancer

There has been more work done on genes that predispose to cancer than on genes associated with any other group of diseases. Molecular biology is useful for other areas of cancer research as well. For instance, molecular markers can improve the quality of epidemiology studies by clarifying disease subgroups. By identifying homogeneous subgroups of disease, stronger associations can be found with the underlying risk factors. Dale Sandler, chief of the Environmental and Molecular Epidemiology Section, has recently completed a study of acute leukemia that demonstrates this principle. Acute leukemias are a mixed group of cancers with diverse causes. Sandler interviewed a large sample of patients and healthy comparison persons about their jobs, hobbies, and medical history. Leukemia patients were classified not only according to clinically important pathologic subtypes, but also by chromosome abnormalities of the blood-forming tissues and by whether or not there was a mutation of the *ras* oncogene. (Specific *ras* gene mutations have been seen with chemical exposures in animal studies.)

Results on smoking show the usefulness of better classification of patients. Smoking was found to be associated in older patients with a twofold increase in risk for acute myeloid leukemia and a threefold risk for acute lymphocytic leukemia. This relation with smoking was even stronger within certain subtypes of leukemia, which may offer clues as to how smoking causes the disease. For example, Sandler has found that smoking is more common among patients with loss of part or all of chromosome 7. Deletion of this chromosome has previously been seen in patients with a history of chemotherapy for other diseases and in patients with occupational exposure to solvents. This suggests that the leukemogenic effect of smoking may be due to chemicals found in cigarette smoke (e.g., benzene).

Similarly, Sandler and her colleagues have found that occupational exposure to solvents is strongly related to mutation of the *ras* oncogene. In this case, the occupational exposure had not been associated with the overall risk of leukemia.

Oncogenes and their relation to environmental exposures are being explored by Jack Taylor, senior clinical investigator. There are at least two classes of genes—oncogenes and tumor-suppressor genes—that seem to be critical targets for environmental agents in cancer initiation and progression. Taylor's strategy is to collect tumors from people with high exposures to known environmental carcinogens and then to look for evidence of damage to specific gene sequences. Taylor has set up collaborations with groups from the United States, Norway, and Canada to collect tumors from persons with unique exposures. The majority of his work has been on lung and bladder cancer, both of which have strong environmental determinants. Taylor has collected bladder tumors from persons exposed to benzidine, β-naphthylamine, cyclophosphamide, and cigarette smoke and is pursuing samples from persons exposed to arsenic, polycyclic aromatic hydrocarbons, and phenacetin. He has collected lung tumors from persons exposed to radon, nickel, asbestos, and cigarette smoke, and is planning projects to collect tumors from people exposed to arsenic and chromium.

Senior staff. (Left to right) Jack Taylor, Dale Sandler, Allen Wilcox, and Freja Kamel.

Many of these samples come from blocks of tissue preserved by pathologists after surgery. Even specimens that are 30 years old or more, retrieved from remote recesses of hospital basements, can provide ample DNA from a single microtome slice of tissue. Using the polymerase chain reaction (PCR) technique, specific genes can be screened and sequenced. By contrasting the pattern of mutations in tumors from people with different exposures, the critical chain of events that lead to environmentally induced cancers can begin to be characterized.

The epidemiologic use of laboratory methods is not new. Today, however, the range of laboratory tools relevant to epidemiology goes far beyond infectious diseases. Epidemiologic projects at NIEHS reflect the spectrum of laboratory methods, from measurement of body burden of toxins to the application of genetic assays, that clarify and strengthen the study of environmental hazards and their effects on human health.

Vision for the Future Sets NIEHS Priorities

"At a time when expanding research opportunities are at odds with tighter budgets, priority setting is a must," says Kenneth Olden, NIEHS director. Two documents will play a key role in priority setting for NIEHS: a recently completed document, NIEHS's *Vision for the Future,* and its companion report which provides the basis for the *Vision* document, the 1992 Report of the Fourth Task Force for Research Planning in Environmental Health Sciences, *Human Health and the Environment: Some Research Needs.*

The National Advisory Environmental Health Sciences Council, a key NIEHS advisory body of scientists and other professionals from outside government, oversaw the development and review of both reports. The task force report was mandated by Congress and prepared by 19 internationally recognized science and public health professionals, co-chaired by Morton Lippmann and Arthur Upton, the deputy director and former director of the Institute of Environmental Medicine, New York University Medical Center, respectively.

The NIEHS's *Vision for the Future* built on the task force report and on input over the past two years from university-based centers and scientists in the field of environmental health sciences, relevant scientific societies, colleagues at NIH and at other federal agencies, industry, and the public.

Vision for the Future describes the NIEHS mission this way:

> Human health and human disease result from three interactive elements: environmental exposures, individual susceptibility and time. The mission of the National